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RISK OF BLADDER CANCER BY SOURCE AND TYPE OF TOBACCO EXPOSURE: A CASE-CONTROL STUDY

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The association between tobacco use and risk of bladder cancer was investigated in a population-based case-control study conducted in Alberta and south-central Ontario, Canada, between 1979 and 1982. In all, 826 histologically-confirmed cancer cases and 792 randomly selected controls, individually matched to cases for age, sex, and area of residence, were recruited into the study. Compared to those who had never smoked cigarettes, males and females who had ever smoked cigarettes had a statistically highly significant 2-fold increase in risk of bladder cancer; for ex-smokers, the risk was intermediate between that for current smokers and never-smokers. There was a dose-dependent increase in risk of bladder cancer with total lifetime cigarette consumption, of similar magnitude for males and females. In males, risk increased with self-reported degree of inhalation in ex-smokers and in current smokers (statistically significant trend), while in females there was no association in current smokers, and a statistically significant inverse association in ex-smokers. Overall, risks of bladder cancer associated with lifetime consumption of plain and filter cigarettes were similar, and there was little evidence to suggest that switching from plain to filter cigarettes was beneficial. Neither passive smoking nor other forms of tobacco consumption (pipes, cigars, chewing tobacco, or snuff) were associated with altered risk of bladder cancer. The population attributable risk for cigarette smoking was about 47% in males and about 33% in females.

Epidemiologic studies of the relationship between tobacco use and bladder cancer have generally suggested that cigarette smoking is causally associated with increased risk, but have provided less conclusive evidence concerning the risk of bladder cancer associated with other forms of tobacco use and with passive smoking (Matanoski and Elliott, 1981; Najem *et al.*, 1982; Cartwright *et al.*, 1983; Mommsen and Aagard, 1983; Vineis *et al.*, 1984, 1988; Morrison *et al.*, 1984; Rebelakos *et al.*, 1985; Sandler *et al.*, 1985; Hartge *et al.*, 1985, 1987; Schifflers *et al.*, 1987; Kantor *et al.*, 1988). Therefore, there is a need for additional investigations of the last 2 issues, while several aspects of the association between cigarette smoking and bladder cancer also require further study, including the nature of the dose-response relationship, the relative magnitude of the effect in males and females, the influence of degree of inhalation, and the effects of different types of cigarettes (filter and non-filter). Of particular interest with respect to type of cigarette are the relative magnitude of the effects of plain (non-filter) and filter cigarettes, and the change in risk on switching from plain to filter cigarettes; large studies are needed to examine these issues and, to date, the only study in which both have been examined is that of Hartge *et al.* (1987), who observed that the risk of bladder cancer was higher for individuals who had smoked plain cigarettes only than for those who had smoked filter cigarettes only, but that changing from plain to filter cigarettes did not lead to a reduction in the risk of bladder cancer. In this paper, we examine the issues outlined above, using data from a large case-control study conducted in Canada.

SUBJECTS AND METHODS

The study methods have been presented in detail elsewhere (Risch *et al.*, 1988*a*) and are described here only briefly.

Cases and controls

Persons eligible for inclusion in the study as cases consisted of all individuals who were diagnosed between 1979 and 1982 with primary, histologically confirmed tumours of urothelial origin, who were resident in the province of Alberta, in metropolitan Toronto or in other parts of south-central Ontario, and who were between 35 and 79 years of age. The term "bladder cancer" as used here includes all bladder tumours of urothelial origin (whether of borderline or full malignancy) as well as all other primary malignant tumours of the bladder. (Patients with recurrent malignant neoplasms of the bladder or invasion of the bladder from primary prostatic cancer were not included.) Cases in northern Alberta were identified through the Cross Cancer Institute, while cases in southern Alberta were identified through the division of the province-wide tumour registry located in Calgary. In south-central Ontario, cases were identified by monthly review of records in hospital departments of surgery, urology, pathology, and of medical records. Of 1,251 eligible cases, 835 (67%) were interviewed, all within one year of diagnosis. Reasons for non-participation of potentially eligible cases (and controls) have been presented elsewhere (Risch *et al.*, 1988*a*).

Controls in both provinces were selected at random from province-wide, annually updated listings, and were matched one-to-one to cases for age (within 4 years), sex and area of residence. Of 1,483 potentially eligible controls, 792 (53%) agreed to participate; of these, 602 were male and 190 were female. By the end of the data collection period, matched controls had not been obtained for 43 cases. Also, interview data showed that errors in dates of birth invalidated the matching for 21 of the existing pairs. Nevertheless, it was possible to match the 21 controls from these last case-control pairs, and 55 of the 64 unmatched cases, either to each other or within the existing case-control pairs. Therefore, 781 matched sets were created, of which 739 were pairs, 35 were triplets, and 4, 2 and 1 comprised 4, 5 and 9 individuals, respectively. The 9 cases which could not be matched were deleted from the analyses; of the remaining cases, 627 were male and 199 were female.

Measurement of exposure

Information was obtained from study subjects by means of an interviewer-administered questionnaire which addressed family, medical, occupational and residential history, socio-economic factors, and intake of various dietary factors. Study

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subjects were also asked about their use of each of the following tobacco products: plain cigarettes, filter cigarettes, cigars, cigarillos, pipes, chewing tobacco and snuff. For each product for which ever use was reported, respondents were asked to indicate their level of consumption by age (*i.e.*, changes in the frequency of consumption with age were noted). These data enabled various indices of use (*e.g.*, total duration of use, years since last use) to be calculated. (Individuals with a lifetime cigarette consumption of less than 185 cigarettes were defined as never-smokers, while ex-smokers were defined as those who had last smoked more than 1 year prior to interview.) Study participants were then asked about the usual extent to which they inhaled the tobacco products that they had used (the options were "deeply", "somewhat", and "not at all"). Finally, they were asked about their exposure to the tobacco smoke of others at home and at work.

Statistical analysis

Conditional logistic regression models (Breslow and Day, 1980) were used to derive maximum likelihood odds ratio (OR) estimates and associated 95% confidence intervals (CI), and to test for the statistical significance of trends in risk. Matching was preserved for the majority of the analyses, but where the number of subjects available for analysis was small, matching was broken and unconditional logistic regression (Breslow and Day, 1980) was used. All of the estimates of effect presented here are adjusted for age (which was introduced into models at a continuous term, even when matching was retained). Additional adjustment for other risk factors for bladder cancer in this study [diabetes diagnosed after the age of 20 years (Risch *et al.*, 1988*a*) and several occupations (Risch *et al.*, 1988*b*)] did not substantially change the point estimates of effect, and the results presented here are derived from models which did not include these variables. The population attributable risk for cigarette smoking was calculated by the method of Bruzzi *et al.* (1985), using risk expressed in terms of log (1 + pack-years).

RESULTS

Several aspects of cigarette smoking history are examined in Table I, which shows little difference between the patterns for males and females. Compared to the risk of bladder cancer for those who had never smoked cigarettes, males and females who had ever smoked cigarettes had a statistically significant 2-fold increase in risk; risk for ex-smokers was intermediate between those for current smokers and for never-smokers. There was an inverse association between age at commencement of smoking and risk of bladder cancer, and some suggestion of increases in risk with duration of smoking and with average number of cigarettes smoked per day. Age at commencement of smoking and duration of smoking were inversely associated with each other, and when they were examined simultaneously (as continuous variables) in a conditional logistic regression model, only the effect for duration remained (data not shown). Duration and frequency of cigarette consumption were combined to give a measure of total lifetime cigarette consumption [expressed as pack-years *i.e.*, average frequency (packs/day) × duration (years)], and there was a positive association between this variable and risk of bladder cancer. A formal test for interaction between total cigarette

TABLE I – RISK OF BLADDER CANCER BY HISTORY OF CIGARETTE SMOKING[1]

Category	Males			Females		
	Number of cases	Number of controls	OR (95% CI)	Number of cases	Number of controls	OR (95% CI)
Never-smoked	61	112	1.0[2]	81	105	1.0[2]
Ever-smoked	566	490	2.08(1.47–2.93)	118	85	1.91(1.24–2.94)
Ex-smoker	287	305	1.67(1.16–2.41)	36	40	1.20(0.69–2.08)
Current smoker	279	185	2.65(1.82–3.86)	82	45	2.62(1.58–4.33)
Age first smoked (years)						
1–14	160	122	2.40(1.60–3.60)	13	7	2.42(0.91–6.39)
15–19	271	222	2.26(1.55–3.29)	50	28	2.66(1.42–4.99)
≥20	135	146	1.63(1.09–2.43)	55	50	1.54(0.94–2.53)
p(trend)		0.025			0.044	
Duration of smoking (years)						
1–10	35	40	1.55(0.89–2.71)	9	16	0.76(0.29–1.99)
11–20	51	60	1.50(0.91–2.49)	11	13	1.14(0.47–2.81)
21–30	91	89	1.84(1.19–2.85)	29	12	3.36(1.44–7.87)
≥31	389	301	2.34(1.63–3.39)	69	44	2.21(1.32–3.70)
p(trend)		<0.001			<0.001	
Average frequency of smoking (cigs./day)						
1–10	102	125	1.49(0.99–2.25)	36	41	1.22(0.69–2.15)
11–20	229	174	2.35(1.61–3.43)	46	27	2.30(1.24–4.28)
21–30	161	122	2.43(1.61–3.65)	36	17	2.88(1.47–5.63)
≥31	74	69	1.95(1.22–3.10)	—	—	—[3]
p(trend)		<0.001			<0.001	
Pack-years of smoking						
1–19	131	162	1.47(0.99–2.19)	48	47	1.39(0.81–2.38)
20–39	184	141	2.36(1.59–3.50)	37	26	1.81(1.00–3.27)
≥40	251	187	2.40(1.64–3.50)	33	12	4.88(2.11–11.27)
p(trend)		<0.001			<0.001	

[1]All cigarettes (plain and filter) combined.–[2]Reference category. Odds ratios are derived from matched analyses, and cannot be calculated directly from the unmatched distribution of cases and controls shown in the Table.–[3]Examined at 4 levels only; the uppermost level being more than 20 cigarettes/day.

consumption and sex was not statistically significant (p = 0.13); similarly, there was no interaction between total cigarette consumption and age (p = 0.33).

A more formal examination of the dose-response relationship is presented in Table IIA (results in the body of this table are for males and females combined). In model I, average frequency and duration were entered as simple linear terms. Both factors had statistically significant positive associations with risk of bladder cancer, and there was no evidence of an interaction between them. Ex-smokers were at reduced risk in relation to current smokers, for a given frequency and duration of use. In the second model in Table IIA, risk was expressed on a logarithmic scale as a function of total cigarette consumption [*i.e.*, log (1 + [average frequency × duration])], and a term for ex-smokers was included in the model. The fit of this model to the data was slightly better than that of model I and, since it employed fewer parameters, it was used to represent the effect of cigarette smoking in subsequent analyses. In general, however, the 2 models give similar predictions of risk (Table IIB). When the analyses were repeated for males and females separately, the results were similar, except for heavy exposures, where risks for females were somewhat higher than the corresponding risks for males (data not shown).

As indicated in Table IIA, those who gave up cigarette smoking were at a lower risk than those who continued to smoke, given the same frequency and duration of cigarette smoking. This effect was examined further by subdividing ex-smokers by time since quitting (Table III). The reduction in risk experienced by ex-smokers appeared to be greatest in the first decade after quitting.

Risk of bladder cancer increased with self-reported degree of inhalation in male cigarette smokers, and decreased in females (Table IV); the latter trend was statistically significant. In males, risk increased with degree of inhalation in both ex- and current smokers [when both categorized variables were introduced into a conditional logistic regression model together with the term log (1 + cumulated pack-years)], and the trend for current smokers was statistically significant. In females, there was an inverse association (statistically significant) between degree of inhalation and risk of bladder cancer in ex-smokers, while the variation in risk with degree of inhalation in current smokers was irregular and not dose-dependent (data not shown).

Risk of bladder cancer increased with lifetime cumulative consumption of both plain and filter cigarettes. This is shown in Table V, which reveals the similarity of risks for the 2 types of cigarettes at corresponding levels of cumulative consumption (although the data shown in the footnote to Table V suggest that the effect of filter cigarettes was slightly stronger than that of plain cigarettes).

There was little evidence to suggest that switching from plain to filter cigarettes conferred benefit in terms of reduction in the risk of bladder cancer (Table VI). Indeed, the risk for subjects who had switched from plain to filter cigarettes was generally higher than that for subjects who had smoked plain cigarettes only.

Risk of bladder cancer was not influenced by the use of pipes, cigars, chewing tobacco or snuff (Table VII). With analyses restricted to subjects who had never smoked cigarettes, the results were practically the same (data not shown).

Table VIII shows results relating to reported exposure to passive smoking. There was no evidence for an effect of passive smoking, even when risk was examined by duration of exposure, and when those who had been exposed both at work and at home were compared with those reporting no exposure (data not shown). Also, passive smoking was not associated with altered risk of bladder cancer in subjects who had not smoked cigarettes (data not shown).

The population-attributable risk for cigarette smoking was about 47% in males, and about 33% in females. For males and females combined, the population-attributable risk for cigarette smoking was about 44%.

DISCUSSION

Potential sources of bias in this study have been discussed in detail elsewhere (Risch *et al.*, 1988*a*), and are reviewed here only briefly. Firstly, the response rate for cases was 67% in both areas of the study, the major reasons for non-participation being subject refusal (14%) and death or severe illness (11%);

TABLE II – DOSE-RESPONSE MODELS AND PREDICTIONS OF THE EFFECT OF CIGARETTE SMOKING[1]

IIA: Dose-response models

Model	Variable	Coefficient	Standard error	p value
I	Average frequency (packs/day)	0.5178	0.2221	0.020
	Duration (years)	0.01806	0.004389	<0.0001
	Average frequency × duration	−0.009889	0.006193	0.11
	Ex-cigarette smoker	−0.2961	0.1258	0.019
II	Log (1 + [average frequency (packs/day) × duration (years)])	0.2396	0.03564	$<10^{-10}$
	Ex-cigarette smoker	−0.2910	0.1112	0.0089

IIB: Predictions of effect

Average frequency (cigs/day)	Duration (years)	Relative risk[2]	
		Model I	Model II
20	20	1.98	2.07
20	40	2.35	2.44
40	20	2.72	2.44
40	40	2.63	2.87

[1]Coefficients shown in the body of the Table are for males and females combined. For males, the coefficients for frequency, duration, frequency × duration, and log [1 + (frequency × duration)], were 0.4925, 0.01919, −0.01079, and 0.2190, respectively; for females, the corresponding coefficients were 0.3270, 0.001742, 0.01840, and 0.3209, respectively.–[2]Risk relative to lifetime non-cigarette smokers for current cigarette smokers of same age and sex.

TABLE III – RISK OF BLADDER CANCER IN CURRENT SMOKERS, AND IN EX-SMOKERS BY YEARS SINCE LAST SMOKED

Category	Males			Females		
	Number of cases	Number of controls	OR[1](95% CI)	Number of cases	Number of controls	OR[1](95% CI)
Never smoked	61	112	1.0[2]	81	105	1.0[2]
Ex-smokers, by years since last smoked:						
>10	68	53	1.37(0.68–2.75)	15	8	0.83(0.19–3.69)
>5 and ≤10	40	54	0.79(0.37–1.65)	7	5	0.69(0.12–4.12)
>1 and ≤5	179	198	1.10(0.64–1.88)	14	27	0.42(0.15–1.16)
Current smokers	279	185	1.55(0.80–2.98)	82	45	0.98(0.29–3.39)
p(trend)[3]		0.16			0.090	

[1]Adjusted for lifetime cigarette consumption [log (1 + cumulated pack-years)].–[2]Reference category. Odds ratios for all subjects are derived from matched analyses and cannot be calculated directly from the unmatched distributions of cases and controls shown in the Table.–[3]For years since last smoked as a continuous variable.

TABLE IV – RISK OF BLADDER CANCER IN CIGARETTE SMOKERS, BY DEGREE OF INHALATION

Category	Males			Females		
	Number of cases	Number of controls	OR (95% CI)	Number of cases	Number of controls	OR (95% CI)
Never smoked	61	112	1.0[1]	81	105	1.0[1]
Ever smoked, and inhaled:						
Not at all	49	57	1.14(0.67–1.96)	28	19	0.90(0.37–2.21)
Somewhat	178	159	1.36(0.85–2.18)	56	35	0.68(0.29–1.61)
Deeply	339	274	1.47(0.91–2.38)	34	31	0.36(0.13–0.97)
p(trend)		0.11			0.028	

[1]Reference category. Odds ratios are derived from matched analyses and cannot be calculated directly from the unmatched distribution of cases and controls shown in the Table. Estimates of effect are adjusted for lifetime cigarette consumption [log (1 + cumulated pack-years)].

for controls, the response rate was 69%. The results presented here may be biased through non-response, although this would have occurred only if response rates by smoking status were different for cases and controls. Secondly, of the 826 cases included in these analyses, 64 had tumours of borderline malignancy, while virtually all of the remaining tumours were classified as transitional-cell or papillary transitional-cell carcinomas. When the analyses were repeated after excluding the 64 cases of borderline malignancy (and their corresponding controls), the results were similar to those presented here. Thirdly, cases and controls may have been misclassified with respect to exposure status, which was determined from interviewer-administered questionnaires. Although some misclassification seems likely, there is little reason to suspect that there were marked differences between cases and controls in the degree of misclassification.

In this study, males and females who had ever smoked cigarettes had a statistically significant 2-fold increase in risk of bladder cancer. The risk for ex-smokers was intermediate between those for current smokers and for never-smokers, and

TABLE V – RISK OF BLADDER CANCER BY LIFETIME CUMULATIVE CONSUMPTION OF PLAIN AND FILTER CIGARETTES[1]

Category	Males			Females		
	Number of cases	Number of controls	OR (95% CI)	Number of cases	Number of controls	OR (95% CI)
Plain cigarettes (pack-years)						
0	126	173	1.0[2]	127	140	1.0[2]
>0 and ≤10	143	146	1.23(0.87–1.75)	35	34	0.95(0.54–1.70)
>10 and ≤25	158	124	1.61(1.13–2.30)	24	12	1.49(0.65–3.41)
>25	200	159	1.72(1.24–2.40)	13	4	2.88(0.85–9.72)
p(trend)		0.013			0.035	
Filter-cigarettes (pack-years)						
0	245	301	1.0[2]	92	116	1.0[2]
>0 and ≤10	100	107	1.14(0.81–1.61)	27	24	1.21(0.59–2.50)
>10 and ≤25	125	91	1.56(1.12–2.16)	43	30	1.68(0.94–3.00)
>25	157	103	1.99(1.43–2.79)	37	20	2.36(1.15–4.84)
p(trend)		5.6×10^{-5}			7.0×10^{-4}	

[1]With lifetime cumulative consumption examined as a continuous variable [*i.e.*, log (1 + total consumption)], the increase in risk with each 10 pack-years of use of plain cigarettes was 1.31 (95% CI 1.11–1.55) for males, and 1.52 (0.91–2.56) for females; the corresponding estimates for use of filter cigarettes were 1.53 (1.28–1.83) and 1.84 (1.23–2.74), respectively. –[2]Reference category. Odds ratios are derived from matched analyses and cannot be calculated from the unmatched distributions of cases and controls shown in the Table.

TABLE VI – RISK OF BLADDER CANCER BY SMOKING STATUS AND BY TYPE OF CIGARETTE EVER SMOKED

Category	Number of cases	Number of controls	OR (95% CI)
Current smokers			
Plain only	42	35	1.0[1]
Switched to filter[2] <15 years ago	174	110	1.36(0.80–2.33)
Switched to filter ≥15 years ago	79	38	1.88(1.00–3.53)
Filter only	66	47	1.35(0.71–2.56)
Ex-smokers, quit <10 years ago			
Plain only	30	29	0.86(0.42–1.75)
Switched to filter	73	72	0.93(0.52–1.64)
Filter only	27	19	1.36(0.62–2.99)
Ex-smokers, quit ≥10 years ago			
Plain only	123	136	0.97(0.56–1.68)
Switched to filter	52	59	0.91(0.49–1.70)
Filter only	18	30	0.67(0.31–1.47)
Never smoked	142	217	0.98(0.48–2.02)

[1]Reference category. Odds ratios are derived from matched analyses and cannot be calculated from the unmatched distribution of cases shown in the Table. Estimates are adjusted for log (1 + cumulated pack-years).–[2]In the categories in which subjects reported switching to filter cigarettes, there were (reading from the first mentioned "switching" category to the last) 3, 5, 5 and 5 cases, respectively, and 2, 0, 3 and 4 controls, respectively.

TABLE VII – RISK OF BLADDER CANCER (IN MEN) ASSOCIATED WITH EVER USE OF PIPES, CIGARS, CHEWING TOBACCO AND SNUFF

Category	Number of cases	Number of controls	OR (95% CI)
Pipe			
Never smoked	485	469	1.0[1]
Ever smoked	142	133	1.03(0.77–1.37)
Cigars			
Never smoked	561	529	1.0[1]
Ever smoked	66	73	0.97(0.69–1.36)
Chewing tobacco			
Never used	601	568	1.0[1]
Ever used	26	34	0.60(0.34–1.06)
Snuff			
Never used	618	584	1.0[1]
Ever used	9	18	0.47(0.21–1.07)

[1]Reference category. Odds ratios are derived from matched analyses and cannot be calculated directly from the unmatched distribution of cases and controls shown in the Table. All estimates of effect are adjusted for lifetime cigarette consumption [log (1 + cumulated pack-years)].

the reduction in risk associated with giving up smoking was greatest in the first decade after quitting. There was some suggestion of an increase in risk with duration and with average frequency of cigarette smoking, and there was a dose-dependent increase in risk of bladder cancer with total lifetime cigarette consumption (*i.e.*, average frequency × duration).

These results are in broad agreement with those of other recent case-control studies of bladder cancer (Najem *et al.*, 1982; Cartwright *et al.*, 1983; Mommson and Aagard, 1983; Vineis *et al.*, 1984; Morrison *et al.*, 1984; Rebelakos *et al.*, 1985; Hartge *et al.*, 1987; Kantor *et al.*, 1988), in which at least some aspects of the association with cigarette smoking have been examined. The consistency of these findings, together with the strength of the association (the relative risk for ever-smokers ranges from about 2 to 5), the dose-response nature of the relationship, the persistence of the association after adjustment for major potential sources of confounding, and its biological plausibility (Wynder and Goldsmith, 1977), strongly suggest that the association is causal. The apparent decrease in risk of bladder cancer on cessation of cigarette smoking suggests a late-stage carcinogenic effect, although the presence of cigarette smoke of compounds capable of inducing bladder cancer in animal experiments (Wynder and Goldsmith, 1977) raises the possibility of an early-stage effect in addition.

For males in this study, risk of bladder cancer increased with self-reported degree of inhalation, and the association was statistically significant in current smokers; in contrast, there was a statistically significant inverse association between degree of inhalation and risk of bladder cancer in female ex-smokers. Morrison *et al.* (1984), in a multi-centre case-control study, observed in each centre a small increase in risk of bladder cancer in male cigarette smokers who inhaled deeply; for females, risk was either increased or decreased, but not significantly so. Although the findings for males seem plausible, the results for females raise doubts about the validity of self-reported degree of inhalation. Stepney (1982), who compared biochemical measures of exposure to cigarette smoke with self-reported degree of inhalation in a group of smokers, concluded that self-reports provided little indication of actual exposure to toxic constituents of smoke, and suggested that this resulted from failure to obtain information on an additional dimension of inhalation, namely its duration. Data on duration of inhalation were not available in the present study, and were not reported by Morrison *et al.* (1984).

The increase in risk with each 10 pack-years of use of filter cigarettes was about 15% higher than that for plain cigarettes. The reason for the stronger effect of filter cigarettes is not clear, but possible explanations include chance, and variation in the effect of cigarette smoking with age (subjects who had smoked filter cigarettes were generally younger than those who had smoked plain cigarettes). Of these, the latter can probably be excluded, since there was no statistical evidence for an age interaction. In contrast to the results of this study, previous comparisons of the risk of bladder cancer associated with use of plain and filter cigarettes have mostly suggested a stronger effect for the former. Thus, Howe *et al.* (1980) and Vineis *et al.* (1984) observed higher risks for users of plain cigarettes, while Cartwright *et al.* (1983) and Hartge *et al.* (1987) reported higher risks of bladder cancer for subjects who had smoked unfiltered cigarettes only than for those who had smoked filtered cigarettes only; in contrast, Morrison *et al.* (1984) found no difference in risk between smokers of filter and plain cigarettes.

This study provided little evidence to suggest that switching from plain to filter cigarettes was beneficial. Hartge *et al.* (1987) (whose analysis we replicated) obtained similar results, while Cartwright *et al.* (1983) observed that the risk of bladder cancer for individuals who had smoked both plain and filter cigarettes was increased, and of similar magnitude to the increase in risk for subjects who had smoked plain cigarettes only. Since filter cigarettes were introduced only in the late 1950s, at the time of our study they had been available for about 20 years. If filter cigarettes have an early-stage carcinogenic effect, then given that the latent interval between exposure to tobacco smoke and development of bladder cancer may be of the order of 20 years or more, it is possible that insufficient time has elapsed to allow the full spectrum of their effects to emerge, and this may account for the apparently paradoxical findings to date.

Other forms of tobacco use (pipes, cigars, chewing tobacco and snuff) were not associated with increased risk of bladder cancer in our study; absence of associations for chewing tobacco and snuff may reflect the small numbers of individuals who reported ever having used these substances. Previous studies have also provided little support for an effect on non-cigarette tobaccos (Matanoski and Elliott, 1981), although 3

TABLE VIII – RISK OF BLADDER CANCER BY HISTORY OF PASSIVE SMOKING

Category	Males			Females		
	Number of cases	Number of controls	OR[1](95% CI)	Number of cases	Number of controls	OR[1](95% CI)
All subjects						
Exposed to smoke of others at home:						
No	123	144	1.0[2]	28	19	1.0[2]
Yes	504	458	1.19(0.88–1.61)	171	171	0.63(0.33–1.21)
Exposed to smoke of others at work:						
No	337	326	1.0[2]	117	114	1.0[2]
Yes	290	276	0.98(0.78–1.24)	82	76	0.87(0.57–1.35)
Non-smokers only[3]						
Exposed to smoke of others at home:						
No	24	40	1.0[2]	15	15	1.0[2]
Yes	37	72	0.94(0.45–1.95)	66	90	0.75(0.33–1.71)
Exposed to smoke of others at work:						
No	36	67	1.0[2]	55	67	1.0[2]
Yes	25	45	0.97(0.50–1.91)	26	38	0.93(0.48–1.79)

[1]Adjusted for lifetime cigarette consumption {log (1 + cumulated pack-years)}.–[2]Reference category. Odds ratios for all subjects are derived from matched analyses and cannot be calculated directly from the unmatched distributions of cases and controls shown in the Table.–[3]Odds ratios for non-smokers only are derived from unconditional logistic regression analyses (adjusted for age in 4 categories, study location in 4 categories, and their interactions).

subgroups of pipe smokers have been reported to have an increased risk of bladder cancer: those who have never smoked cigarettes (Morrison *et al.*, 1984), those who inhale deeply (Howe *et al.*, 1980), and those who have never smoked cigarettes and who inhale deeply (Hartge *et al.*, 1985). Despite the plausibility of associations between cigar and pipe smoking and risk of bladder cancer [since the smoke of both types of tobacco contains many of the same substances as that of cigarette tobacco (Hartge *et al.*, 1985)], it has been suggested that their effect is likely to be small (Morrison *et al.*, 1984), which presumably accounts for the inconclusive nature of findings to date.

Mutagens have been detected in the urine of passive smokers (Bos *et al.*, 1983). Therefore, it seems plausible to suggest that individuals exposed to environmental tobacco smoke might be at increased risk of bladder cancer. However, given that the association between passive smoking and lung cancer appears to be relatively weak (Fielding and Phenow, 1988), it does not seem likely that any association between passive smoking and bladder cancer will be strong. Thus, the absence of an association in this study, and in the smaller study of Sandler *et al.* (1985), is not surprising.

In summary, the results of our study provide strong support for a causal relationship between cigarette smoking and the occurrence of bladder cancer. Furthermore, they suggest that switching from plain to filter cigarettes does not reduce risk, and provide little support for effects of other forms of tobacco use or for passive smoking. From this study it can be estimated that about 47% of bladder cancer in males, and about 33% of that in females, can be accounted for by cigarette smoking. Thus, further attempts should be made to identify the remaining contributors to bladder cancer risk, particularly in females.

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